REMARKS

Status of the Claims

Claims 1, 3 and 7 are pending. Claims 1, 3 and 7 are rejected. Claim 1 is amended herein. Claims 2, 4-6 and 8-22 are canceled. No new matter has been added.

Claim amendments

Claim 1 is amended to clarify that the dose of the high specific alpha particle-emitting isotope-labeled antibody is sufficient to bind to a plurality of sites on a tumor cell such that a minimum of one atom of the isotope delivers at least one alpha particle to the tumor cell to which it binds. No new matter was added in this amendment.

The 35 U.S.C. §103(a) rejection

Claims 1,3 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson** *et al.* (Cancer Res., 50(3 Supp): 9855-9885 (1990)), of record, in view of **Kasperson** *et al.* (*Nuclear Med Comm*, 16, pp. 468-476 (1995)), of record, **Lemelson** (U.S. Patent No. 4,665,897) and **Blankenberg** *et al.* (U.S. Patent No. 6,197,278) or **Vieria** (Eur J Surgical Oncology, 22(4): 331-334 (1996)), and further in view of **Goldenberg** (U.S. Patent No. 4,444,744). Applicant respectfully traverses this rejection.

The Examiner maintains that **Simonson** *et al.* teach intraperitoneal administration of 212-Bi-labeled antibodies specific for the mucin antigen TAG-72 into mice previously injected with LS1744% cells which grow both as solid tumors and ascites in mice. The mice develop ascites at about 20 days after injection of the tumor cells (p. 985s, 2nd col., last PP), and only after developing solid tumor (p. 987s, 2nd col., 1st PP). The Examiner states that **Simonson** *et al.* teach that the specific activity of the labeled antibody is 5-10 μCi/μg which is within the range of the claimed specific activity. The Examiner also states that **Simonson** *et al.* teach that a 56% decrease in tumor mass is obtained with single and repeated administration of Bi-212 labeled antibody in tumors 13 days after injection with 3 gm average tumor mass (p. 986s, 1st col., 3es PP; Fig. 1). The Examiner additionally states that **Simonson** *et al.* teach that the efficacy of the treatment would be even better if the radiolabeled antibody recognizes a cell surface antigen on the target cell rather than the secreted mucin antigen TAG-72 (p. 987s, 2nd col.)

The Examiner also maintains that **Kasperson** *et al.* teach that Bi-213 can be an alternative to Bi-212 with the advantage of safer and easier production (pg. 475, 1st col., 1st PP). The Examiner additionally maintains that **Lemelson** teaches a method of treating tumors by administering antibodies containing inactive nuclide that are rendered radioactive with externally generated radiation, including alpha particles (claim 27) which steps are

repeated as many times as necessary to effect remission or destruction of tumors (claims 28, 35,36).

The Examiner states that **Vieira** *et al.* teach that imaging of breast cancer tissues could begin 10 minutes after intravenous administration of radiolabeled monoclonal antibodies which means the radiolabeled monoclonal antibodies could reach the breast cancer tissues within minutes after its intravenous administration. The Examiner additionally states that **Blankenberg** *et al.* teaches that, after i.v. administration, localization of a radiolabeled high-affinity targeting protein annexin in the target tissue is obtained in only a few minutes (cols. 9-10, last two bridging paragraphs). The Examiner states that **Goldenberg** teaches the use of radiolabeled antibodies to cancer cell surface antigens for cancer immunotherapy.

The Examiner argues that **Simonson** *et al.* do not teach a method of killing a tumor greater than 1 mm in size by intravenously administering Bi-213-labeled antibodies at a dose of about 0.1 mg/m2 to about 10 mg/m2 adequate to deliver a minimum of 1 alpha track per cell. However, the Examiner does state that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention to treat tumors of at least 1 mm in size using the method of **Simonson** *et al.* by administering an antibody labeled with Bi-212. The Examiner states one would have expected that the size of solid tumors taught by **Simonson** *et al.* have an average weight of 3 gm and are advanced tumors after 13 days growth. Additionally, the Examiner states it would have been obvious to administer the labeled antibody once or repeatedly, as

taught by **Simonson** *et al.* and **Lemelson**, to ensure destruction of the tumors. Furthermore, the Examiner states that determination of the optimum dosage is within the level of ordinary skill in the art.

The Examiner also states it would have been obvious to substitute Bi-212 with Bi-213 because **Kasperson** *et al.* teaches Bi-213 is safer and easier to produce. The Examiner also states it would have been obvious to replace antibodies specific for the secreted mucin antigen TAG-72 taught by **Simonson** *et al.* with an antibody that targets a membrane cancer specific antigen on cancer cells as suggested by **Simonson** *et al.* because it would be more efficacious and because antibodies specific for cancer specific antigens on cancer cell surface for use in cancer immunotherapy are well known in the art as taught by **Goldenberg**.

The Examiner argues it would have been obvious to administer the labeled antibody intravenously because it a routine route of administration of labeled antibodies for immunotherapy. One would expect that a Bi-212 or Bi-213 radiolabeled antibody would reach the target cancer cells within minutes after its intravenous administration and that the Bi-212 or Bi-213 –labeled antibody would have ample time to kill target cancer cells despite the relative sort half life of Bi-12 or Bi-213 because **Vieira** *et al.* and **Blankenberg** *et al.* teach that radiolabeled antibody or annexin reach target cancer cells within minutes after i.v. administration.

Simonson *et al.* teaches that Bi-212 may be appropriate for the treatment of peritoneal implant metastases and ascitic cancer when

administered intraperitoneally. The use of a Bi-212 labeled B72.3 antibody against the human colon carcinoma cell line LS174T in a murine model is examined (pg. 985s, first col., last paragraph to second col., second paragraph). The specific activity of the labeled antibody was 5-10 μCi/μg. **Simonson** *et al.* demonstrate that a single i.p. injection of 450 μCi or 3 consecutive i.p. injections of 190 μCi 13 days after tumor inoculation reduced tumor mass by 56%. These tumors were considered to be well advanced (pg. 986s, first col., third paragraph). In a model using smaller tumors four consecutive i.p. doses starting at day 8 of either 90 μCi or 180 μCi reduced tumor mass on average 85% with all mice in any regimen demonstrating some toxicity (pg. 986s, first col., fifth paragraph).

Kasperson *et al.* examined the cytotoxicity of $Bi^{-}213$ *in vitro* and Ac-225 immunoconjugates against the human carcinoma cell lines A431 and SW1398. The reference discloses that Bi^{-213} may be substituted for Bi-212 for the treatment of single cell malignancies (pg. 475, col. 1, line 3). In an in vivo spheroid model no specific cell-killing was observed using up to 1.2 μCi Bi-213 on spheroids with diameters of 0.4 mm to 0.7 mm. **Kasperson** *et al.* state that Bi-213 may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph).

Lemelson teaches methods of detecting, monitoring and treating a tumor by administering a drug unit comprising a monoclonal antibody and a normally nonradioactive or inactive nuclide. The inactive nuclide such as boron-

10 is activated by external radiation such as neutron radiation which in high levels can cause the inactive nuclide to emit a radioactive particle, e.g., alpha, beta or gamma. The inactive nuclide/antibody is administered again, activated and the monitoring process repeated until treatment ceases (Abstract; col. 12, lines 1-69; col. 13, lines 1-28).

Blankenberg *et al.* teach a method of imaging regions of cell death in a mammal using radiolabeled annexin V for gamma ray imaging (Abstract; col. 1, ll. 12-15). Radiolabeled annexin may be administered intravenously (col. 9, ll. 25-28) and imaging generally begins after most of the radiolabeled annexin V has localized to its target which for i.v. administration is about 30-70 minutes (col. 9, ll. 66 to col. 10, ll. 3). If the target is easily accessible such as injured blood vessels, localization may take only a few minutes (col. 10, ll. 7-13). Annexin V is not an antibody, but rather a protein isolated from tissue that binds to phosphatidylserines released from or exposed on the cytoplasmic side of cell membranes damaged due to apoptosis or necrosis of the cell.

Vieira *et al.* teach the use of 99mTc-tetrofosmin as a gamma ray imaging agent to differentiate benign from malignant lesions in breast tissue. Imaging commences 10 minutes after injection (Abstract). However, contrary to the Examiner's statement, **Vieira** *et al.* only state that radiolabeled monoclonal antibodies are an example of a potential imaging agent already under investigation as a means of detecting breast cancer. In the Abstract, **Vieira** *et al.* specifically investigate 99mTc-labeled tetrofosmin, that is 99mTc-ethoxy-ethyl

phosphinoethane, which is a lipophilic, cationic chemical compound and not a radiolabeled monoclonal antibody.

Goldenberg teaches a method of using antibodies highly specific to cell surface antigens that are radiolabeled for tumor localization and detection or for tumor therapy (Abstract). The antibodies are preferably labeled with the gamma emittor, I-131, for radiotherapeutic applications, but may be labeled with alpha emittors, preferably Sc-47, or beta emittors (col. 12, ll. 21-34).

In considering the combination of the prior art, the Examiner states that one of ordinary skill in the art would have been motivated to treat tumors being at least 1 mm in size using an antibody labeled with Bi-213 that targets a specific binding site on tumor cells with a reasonable expectation of success. One of ordinary skill in the art may be motivated by the combination of prior art cited by the Examiner to treat tumors at least 1 mm in size with Bi-213-labeled antibodies with, perhaps, might have a reasonable expectation of success in reducing tumor burden thereby. However, Applicants strongly submit that a reasonable expectation of killing such a tumor is only found in the instant application.

Applicants refer to prior arguments and reiterate that the claims do not recite a method where Bi-213 having any specific activity within the claimed range would kill any large tumor greater than 1 mm in diameter. It is a key element of the instant invention, as recited in the claims, that the specific activity must be high enough and the dose of antibody sufficient to have one atom of the isotope deliver at least one alpha to each cell to which it binds (pg. 13, ll. 16 to

pg. 14, ll. 9). Amended claim 1 recites that the specific activity is selected from within the 0.1-30 mCi/mg range and not that the specific activity may be any value within the range for any construct. As such, amended claim 1 is not drawn solely to a specific alpha-emittor, such as Bi-212 or Bi-213, rather one of ordinary skill in the art selects an alpha-emittor and a specific activity within a range of about 0.1 mCi/mg to about 30 mCi/mg so that the resultant construct can kill the target tumor cell as described.

To make an appropriate selection one of ordinary skill in the art must consider (1) the number of receptor targets (binding sites) on the target cell; (2) the stability of the ligand at the site once targeted; (3) the rapidity by which the ligand reaches the target site; (4) the affinity of the ligand for its target; and (5) the total number of target sites or non specific binding sites in the host (patient) in order to achieve reliable cell kill. As the method has been discussed in previous submissions, Applicants' respectfully refer the Examiner to the specification for a detailed description of the method (pg. 13, ll. 16 to pg. 17, ll. 17), however, in summary, reiterate herein that generally for a Bi-213 labeled antibody targeted to a receptor comprising about 10,000 binding sites on the tumor cell, a minimum specific activity of 10 mCi/mg is required to provide one alpha into each cell provided that the amount of antibody having this specific activity is sufficient to saturate all the available binding sites on the tumor cells available for targeting. Repeated delivery would saturate the available binding sites on the next layer of tumor cells after killing the tumor cells available for

targeting on the previous layer thereby killing the solid tumor (pg. 48, ll. 1-12; Fig. 2).

Failure to use this level of specific activity would result in most cells receiving no radioactive atoms and hence could not adequately kill the target as compared to normal tissues. Specific activities of 3-10 μCi/μg, equivalent to 3-10 mCi/mg Bi-212-labeled antibody taught in **Simonson** *et al.* are insufficient to kill a tumor because **Simonson** *et al.* teach that no cure was achieved even with repeated administrations (pg. 987s, second col., first paragraph). The instant specification teaches that killing a tumor to achieve a cure or at least 5-year disease-free survival means that the probability of killing all tumor cells must approach 1, i.e., killing a tumor means reducing the number of tumor cells to 1 or none. At the time of the instant invention, the specification discloses that all previously described alpha emitting constructs were of such low specific activity that an antibody labeled with such would have yielded ineffective agents or agents unable to induce cures when injected into humans (pg. 20, ll. 13-16). The specification further teaches that potency of treatment is critical to effect a cure which requires an alpha-emitting antibody construct having a sufficiently high specific activity, as discussed herein.

Furthermore, in considering dependent claim 7, selection of dose is not routine for one of ordinary skill in the art. As with the selection of specific activity, the dose of antibody must be sufficient for a minimum of one atom of isotope to deliver at least one alpha per tumor cell (pg. 16, ll. 17 to pg. 17, ll. 1).

The claims recite that the dose of antibody having a specifically selected specific activity may be limited to an appropriate dose within the range recited in claim 7, not that any dose within the range is suitable. Determination of dose also only is found in Applicants' specification, as discussed *supra*.

Therefore, even should one of ordinary skill in the art be motivated to produce and repeatedly administer a Bi-212 or Bi-213-labeled antibody to target tumor cells on a solid tumor at least 1 mm in diameter by the teachings and/or suggestions in **Simonson** *et al.*, **Kasperson** *et al.* and **Lemelson**, no guidance is given as to how to select appropriate specific activities and antibodies such that the radiolabeled antibody provides a minimum of one atom of isotope to deliver at least one alpha per tumor cell to kill the tumor. The inventive concept in Applicants' invention in the method of killing a solid tumor is designing the alpha-emitting radiolabeled antibody as described, not simply administering a Bi-212, Bi-213 or any alpha-emittor one or more times via targeting tumor cells with a cell specific antibody. Such guidance is only found in Applicants specification and therefore, one of ordinary skill in the art merely would be trying which is not the standard under 35 U.S.C. §103(a). As such, any reasonable expectation of success in killing the tumor also is found only in Applicants' specification.

Furthermore, when determining a *prima facie* case of obviousness, what must be considered is what is fairly taught by the prior art. One cannot pick and choose elements without giving due consideration to how these elements function within the context of the invention. Respectfully, the Examiner is picking

and choosing from **Simonson** *et al.*, **Kasperson** *et al.* and **Lemelson** and not considering how these references teach away from the instant invention.

The Examiner states that it would be obvious to administer the labeled antibody once or repeatedly, as taught by **Simonson** *et al.* and **Lemelson**, to ensure destruction of the tumors. **Simonson** *et al.* state that despite a prolonged survival in some of the mice and significant reduction in tumor burden, a cure in none of them was obtained even with administration of 4 x 180 μCi on consecutive days to a tumor 8 days after inoculation (pg. 987s, second col., first paragraph). **Lemelson** teaches a method of repeated treatment with controlled radiation to incrementally destroy tumor cells until the tumor is destroyed (col. 11, ll. 18-32). Cell killing radiation is controlled by administering a non-radioactive stable nuclide-labeled antibody, which only becomes radioactive upon delivery of activating radiation thereto, as described *supra*. Applicants submit that using a nonradioactive nuclide to label an antibody, regardless of the type of radiation or particle emitted upon activation thereof or that the nuclide labeled antibody may be administered repeatedly, in **Lemelson** teaches away from a high specific activity Bi-212 or Bi-213-labeled antibody. Although the non-radioactive nuclides in **Lemelson** may be activated to emit alpha particles, Applicants' specification only teaches and the claims only encompass radioactive alpha emittors *per se*.

The Examiner also states that one of ordinary skill in the art would be motivated to replace Bi-212 in **Simonson** *et al.* with Bi-213 because

Kasperson *et al.* teach that Bi-213 is safer and easier to produce. However, **Kasperson** *et al.* also teach that that Bi-213 may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph). Even though **Kasperson** *et al.* do not preclude using Bi-213 for a solid tumor, one of ordinary skill in the art merely would be trying in replacing Bi-212 with Bi-213 in view of this statement.

Furthermore, the deficiencies found in the combination of **Simonson** *et al.*, **Kasperson** *et al.* and **Lemelson** are not remedied by the inclusion of **Blackenberg** *et al.* or **Vieira** *et al.* and **Goldenberg** in the combination. It is known in the art, for example, as taught in **Goldenberg**, that antibodies specific for cancer specific antigens on cancer cell surfaces may be useful in cancer immunotherapy and that intravenous administration is a standard route of delivery which can effect faster delivery of cancer specific antibodies to tumor vasculature for extravasation. It is also known in the art that time for an antibody to extravasate the tumor vasculature, target the tumor tissue and internalize, if the antibody is internalizable, is dependent on at least the specific antibody used.

Neither **Blackenberg** *et al.* nor **Vieira** *et al.* teach administration of radiolabeled antibodies specific for cancer cells, as discussed *supra*, and at best these references teach that different radiolabeled, e.g., gamma emittors Tc-99, compositions or compounds suitable for imaging localize to different tissues, including tumor tissue, over different time periods. None of these references provide the teaching or suggestion lacking in **Simonson** *et al.* in combination with **Kasperson** *et al.* and **Lemelson** that to kill a tumor a specific

activity for Bi-212 or Bi-213, or even for any other suitable radioactive alpha emittor, must be selected high enough such that a suitable dose of the selected specific antibody labeled with Bi-212 or Bi-213 can provide a minimum of one atom of isotope to deliver at least one alpha particle per tumor cell to which it binds. Again Applicants strongly reiterate that at best one of ordinary skill in the art would be trying without a reasonable expectation of success in killing the tumor not found in Applicants' specification.

Applicants submit that the combination of **Simonson** *et al.*, with **Kasperson** *et al.*, **Lemelson**, **Blackenberg** *et al.* or **Vieira** *et al.*, and **Goldenberg** does not render amended claim 1 prima facie obvious. At a minimum, without a suggestion or teaching to guide one of ordinary skill in the art in the selection of a high specific activity alpha emittor-labeled antibody sufficient whereby a minimum of one atom delivers at least one alpha particle to each available tumor cell in one or more administrations thereto, no reasonable expectation of success in killing the tumor is found. Furthermore, dependent claims 3 and 7 depend from amended claim 1 and limit the alpha emitting isotope and, as discussed *supra*, the dose of the antibody, respectively. As the combination of **Simonson** *et al.*, with **Kasperson** *et al.*, **Lemelson**, **Blackenberg** *et al.* or **Vieira** *et al.*, and **Goldenberg** does not render amended claim 1 obvious, then neither can dependent claims 3 and 7 be rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 3 and 7 under 35 U.S.C. §103(a) be withdrawn.

Applicants submit that amended claims 1, 3 and 7 are in condition for allowance. Accordingly, Applicants request that claims 1, 3 and 7 be passed to issuance. This is intended to be a complete response to the Office Action mailed October 21, 2004. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe that no fees are due, however, should this be in error, please debit Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: Jan 19, 2005

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
BADLER1@houston.rr.com